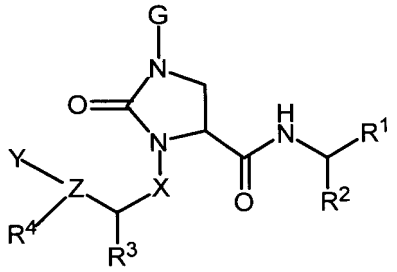
Claims

What is claimed is:

1. A compound, including enantiomers, stereoisomers, rotamers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula I:



Formula I

wherein:

R^1 is COR^5 or $B(OR)_2$, wherein R^5 is selected from the group consisting of: H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, and COR^7 with R^7 being H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10} , wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, R', R^{11}, R^{12}, and R^{13} are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is O, N, or CH;

X is selected from the group consisting of: C=O, C=S and $(CRR')_p$;

p is a number from 1-6;

G is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, alkyl-aryl and alky-heteroaryl with the proviso that G may be additionally optionally and chemically-suitably substituted with U^{11} or U^{12};

R, R^2, and R^3 may be the same or different and are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8

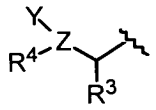
heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

R^4 maybe present or absent, and if R^4 is present, R^4 is selected from H, alkyl, aryl; and

Y is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, and U, where U is selected from alkyl-aryl, aryl-heteroaryl, alkyl-heteroaryl, alkylcarbonyl, arylalkylcarbonyl, arylcarbonyl, heteroalkylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, alkyloxycarbonyl, alkyl-aryloxycarbonyl, aryloxycarbonyl, arylalkyloxycarbonyl, heteroaryloxycarbonyl, heterocycloalkyloxycarbonyl, cycloalkyloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkyl-arylaminocarbonyl, arylaminocarbonyl, arylalkylaminocarbonyl, heteroarylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, alkylsulfonyl, arylsulfonyl, alkyl-arylsulfonyl, arylalkylsulfonyl, heteroarylsulfonyl, cycloalkylsulfonyl, and heterocycloalkylsulfonyl with the proviso that U may be additionally optionally and chemically-suitably substituted with U^{11} or U^{12}; where

U^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that U^{11} may be additionally optionally substituted with U^{12}; and

U^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from U^{12}; and that said moiety:



may alternately represent an arylalkyloxy group;

with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate.

2. The compound of claim 1, wherein R^1 is COR^5, and R^5 is H, OH, $COOR^8$, and $CONR^9R^{10}$.

3. The compound of claim 2, wherein R^1 is $COCONR^9R^{10}$, and is R^9 is H, and R^{10} is H, CH_2-CH=CH_2, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})$ $CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$.

4. The compound of claim 3, wherein R^{10} is CH_2-CH=CH_2.

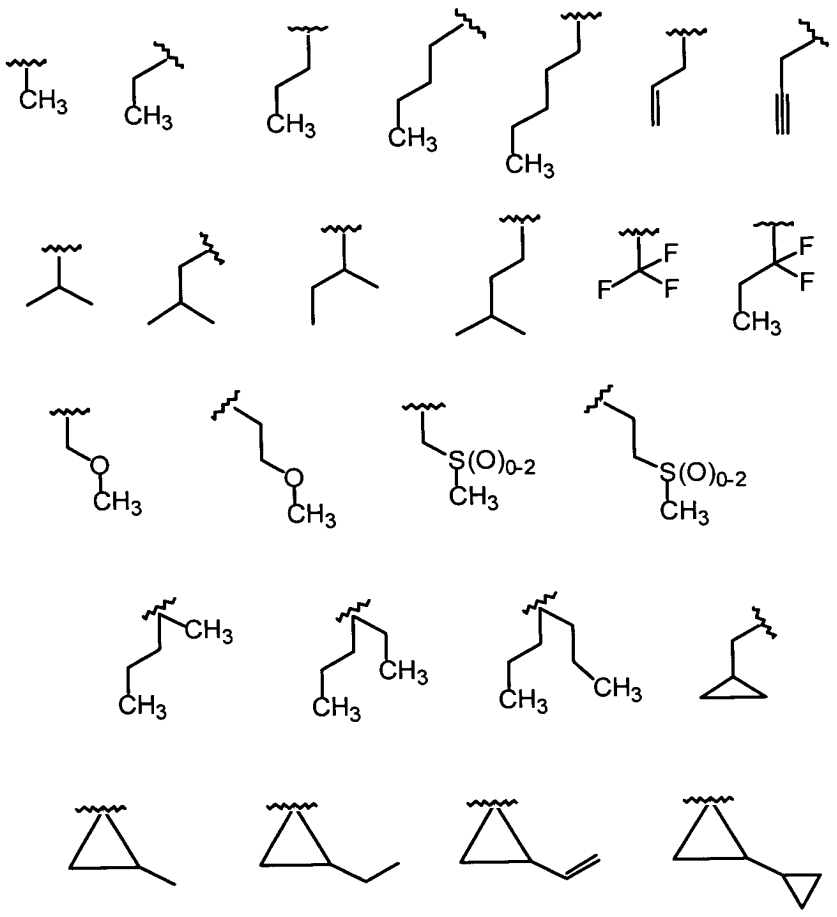
5. The compound of claim 3, wherein R^{10} is $CH(R^{1'})COOR^{11}$.

6. The compound of claim 5, wherein $R^{1'}$ is H and R^{11} is H, allyl or benzyl.

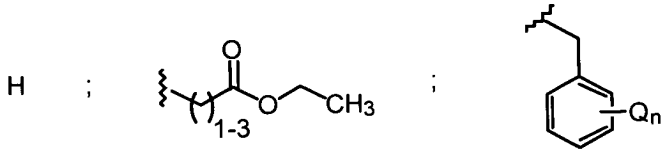
7. The compound of claim 3, wherein R^{10} is $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein $R^{1'}$ is H and $R^{2'}$ is phenyl, substituted phenyl, heteroatom-substituted phenyl, thiophenyl, cyclohexyl, cyclopentyl, cyclopropyl, piperidyl and pyridyl.

8. The compound of claim 3, wherein R^{10} is selected from the group consisting of $CH_2CONHCH(Ph)COOH$, $CH_2CONHCH(Ph)CONH_2$, $CH_2CONHCH(Ph)CONMe_2$ and $CH_2CONHCH(Ph)COO$-benzyl.

9. The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties:



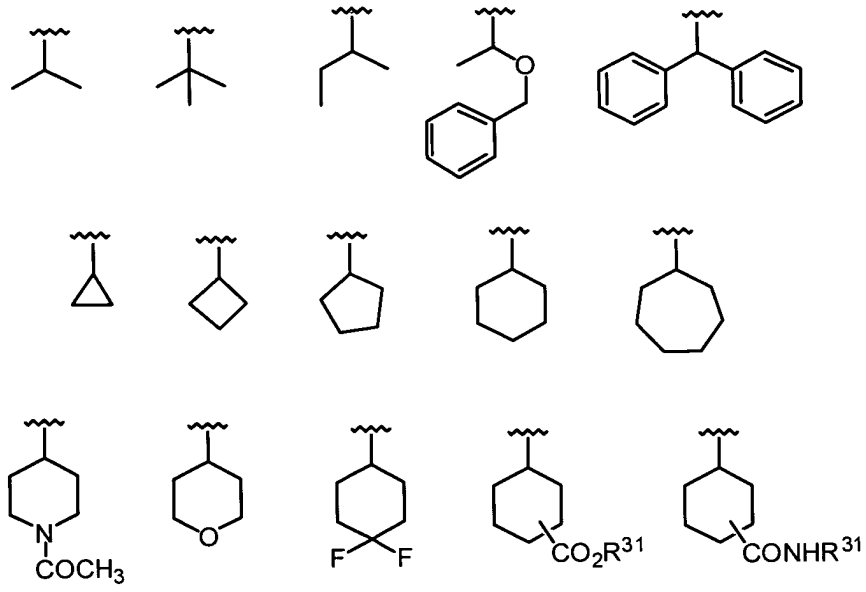
10. The compound of claim 1, wherein G is selected from the group consisting of:



wherein n is a number from 0-2 and Q is selected from the group consisting of Cl, Br, methyl, methoxy, tert-butyl and combinations thereof.

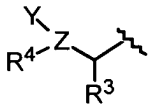
11. The compound of claim 1, wherein X is C=O.

12. The compound of claim 1, wherein R^3 is selected from the group consisting of:



wherein R^{31} = H, alkyl or aryl.

13. The compound of claim 1, wherein said moiety:



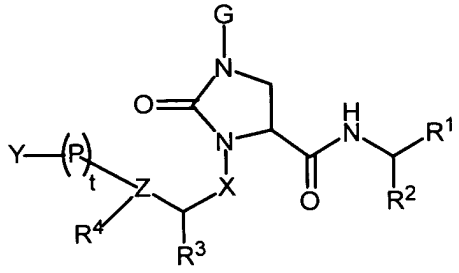
represents an arylalkyloxy group.

14. The compound of claim 13, wherein said arylalkyloxy group is benzyloxy.

15. The compound of claim 1, wherein Z is N and R^4 is H.

16. The compound of claim 1, wherein Y is selected from the group consisting of H, acetyl, or alkoxycarbonyl.

17. A compound, including enantiomers, stereoisomers, rotamers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula II:

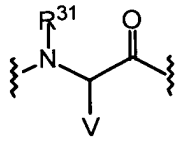


Formula II

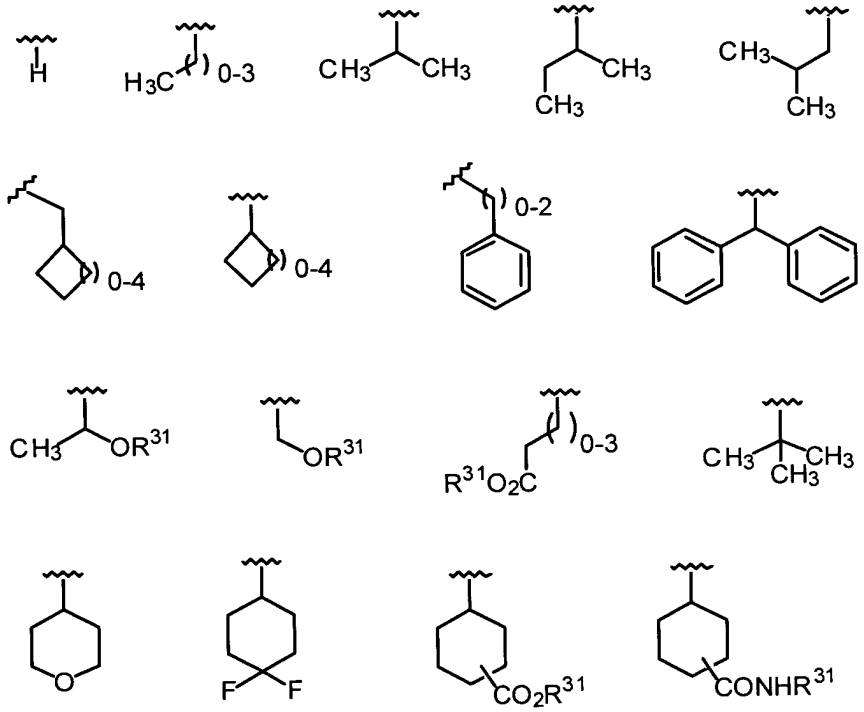
wherein:

t is a number from 1 to 3; and when t is 2 or 3, the P moieties may be the same or different;

P is represented by:



wherein V is selected from the group consisting of the following:



wherein R^{31} is independently selected from H, alkyl or aryl;

R^1 is COR^5 or $B(OR)_2$, wherein R^5 is selected from the group consisting of: H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, and COR^7 with R^7 being H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10} , wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, R', R^{11}, R^{12},

and R^{13} are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is O, N, or CH;

X is selected from the group consisting of: C=O, C=S and $(CRR')_p$;

p is a number from 1-6;

G is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, alkyl-aryl and alky-heteroaryl with the proviso that G may be additionally optionally and chemically-suitably substituted with U^{11} or U^{12};

R, R^2, and R^3 may be the same or different and are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

R^4 maybe present or absent, and if R^4 is present, R^4 is selected from H, alkyl, aryl; and

Y is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, and U, where U is selected from alkyl-aryl, aryl-heteroaryl, alkyl-heteroaryl, alkylcarbonyl, arylalkylcarbonyl, arylcarbonyl, heteroalkylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, alkyloxycarbonyl, alkyl-aryloxycarbonyl, aryloxycarbonyl, arylalkyloxycarbonyl, heteroaryloxycarbonyl, heterocycloalkyloxycarbonyl, cycloalkyloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkyl-arylaminocarbonyl, arylaminocarbonyl, arylalkylaminocarbonyl, heteroarylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, alkylsulfonyl, arylsulfonyl, alkyl-arylsulfonyl, arylalkylsulfonyl, heteroarylsulfonyl, cycloalkylsulfonyl, and heterocycloalkylsulfonyl with the proviso that U may be additionally optionally and chemically-suitably substituted with U^{11} or U^{12}; where

U^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that U^{11} may be additionally optionally substituted with U^{12}; and

U^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from U^{12};

with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate.

18. The compound of claim 17, wherein R^1 is COR^5, and R^5 is H, OH, $COOR^8$, $CONR^9R^{10}$.

19. The compound of claim 18, wherein R^1 is $COCONR^9R^{10}$, and is R^9 is H, and R^{10} is H, CH_2-CH=CH_2, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})$ $CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$.

20. The compound of claim 19, wherein R^{10} is CH_2-CH=CH_2.

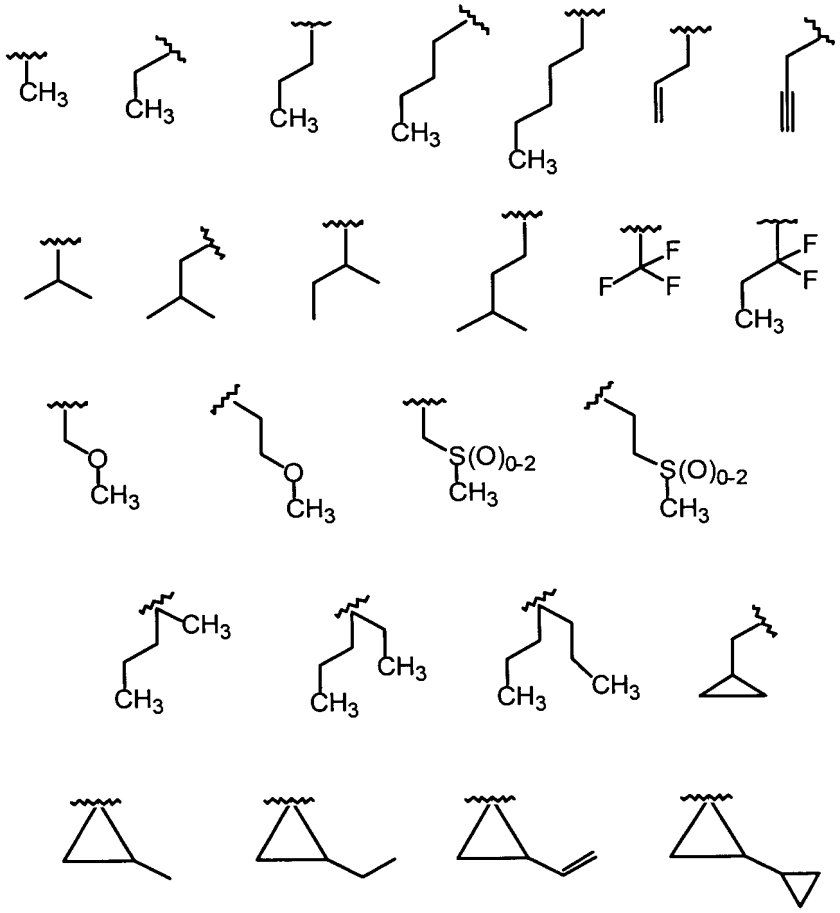
21. The compound of claim 19, wherein R^{10} is $CH(R^{1'})COOR^{11}$.

22. The compound of claim 21, wherein $R^{1'}$ is H and R^{11} is H, allyl or benzyl.

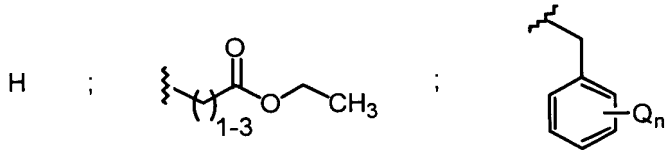
23. The compound of claim 19, wherein R^{10} is $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein $R^{1'}$ is H and $R^{2'}$ is phenyl, substituted phenyl, heteroatom-substituted phenyl, thiophenyl, cyclohexyl, cyclopentyl, cyclopropyl, piperidyl and pyridyl.

24. The compound of claim 19, wherein R^{10} is selected from the group consisting of $CH_2CONHCH(Ph)COOH$, $CH_2CONHCH(Ph)CONH_2$, $CH_2CONHCH(Ph)CONMe_2$ and $CH_2CONHCH(Ph)CO$-O-benzyl.

25. The compound of claim 17, wherein R^2 is selected from the group consisting of the following moieties:



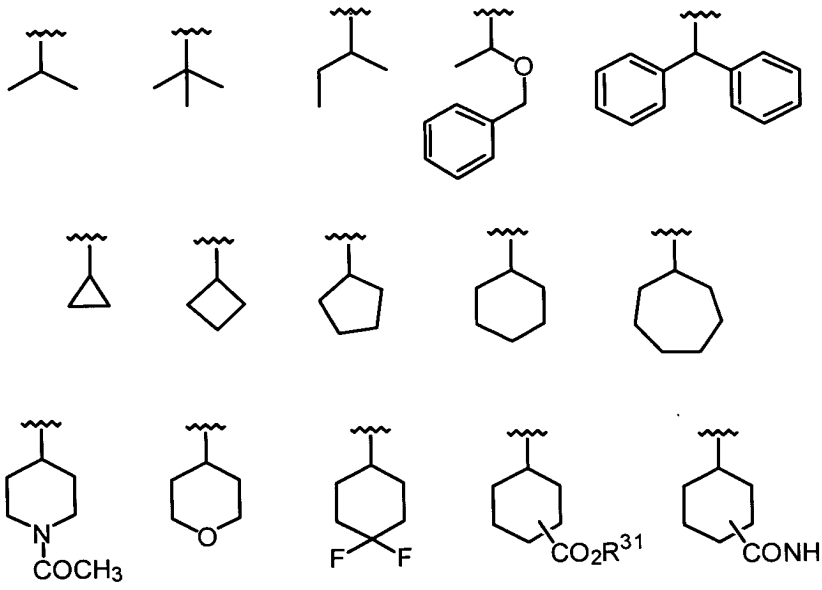
26. The compound of claim 17, wherein G is selected from the group consisting of:



wherein n is a number from 0-2 and Q is selected from the group consisting of Cl, Br, methyl, methoxy, tert-butyl and combinations thereof.

27. The compound of claim 17, wherein X is C=O.

28. The compound of claim 17, wherein R^3 is selected from the group consisting of:



wherein R^{31} = H, alkyl or aryl

29. The compound of claim 17, wherein Z is N and R^4 is H.

30. The compound of claim 17, wherein P is a peptide moiety selected from Glu(O^{t}Bu)-Glu(O^{t}Bu)-Val and Glu-Glu-Val.

31. The compound of claim 17, wherein P is an amino acid moiety selected from Val, Glu(O^{t}Bu) and Glu.

32. The compound of claim 17, wherein t is 1.

33. The compound of claim 17, wherein t is 3.

34. The compound of claim 17, wherein Y is selected from the group consisting of H, acyl, or alkoxycarbonyl.

35. The compound of claim 34, wherein the acyl group is acetyl group.

36. A pharmaceutical composition comprising as an active ingredient a compound of claim 1 or claim 17.

37. The pharmaceutical composition of claim 36 for use in treating disorders associated with HCV.

38. The pharmaceutical composition of claim 36 additionally comprising a pharmaceutically acceptable carrier.

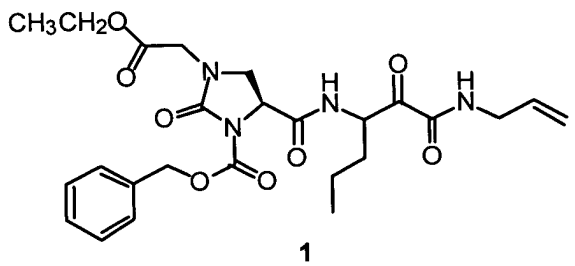
39. A method of treating disorders associated with the HCV protease, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of a compound of claim 1 or claim 17.

40. The method of claim 39, wherein said administration is subcutaneous.

41. The use of a compound of claim 1 or claim 17 for the manufacture of a medicament to treat disorders associated with the HCV protease.

42. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV protease, said method comprising bringing into intimate contact a compound of claim 1 or claim 17 and a pharmaceutically acceptable carrier.

43. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:



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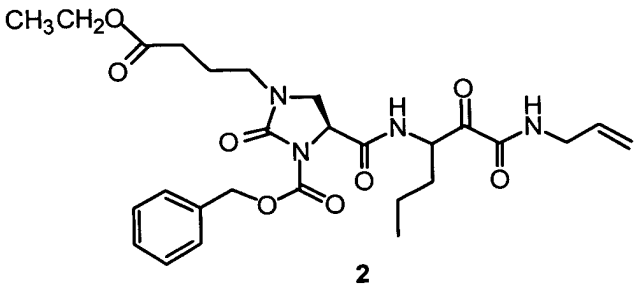

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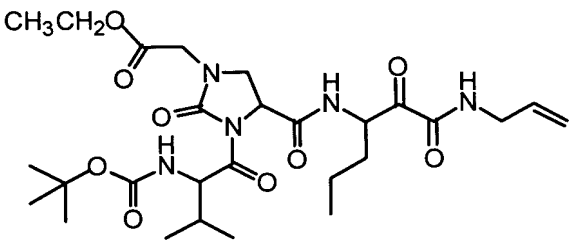

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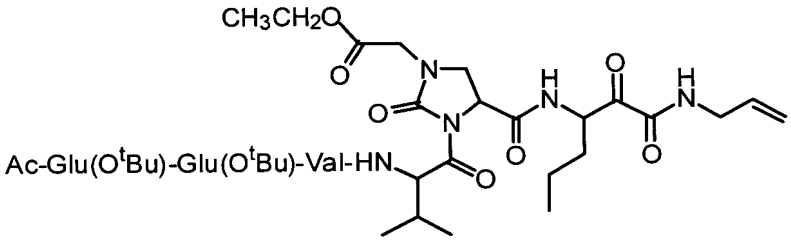

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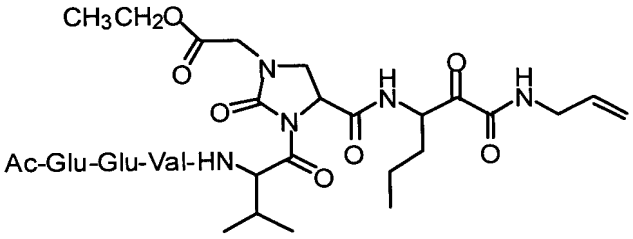

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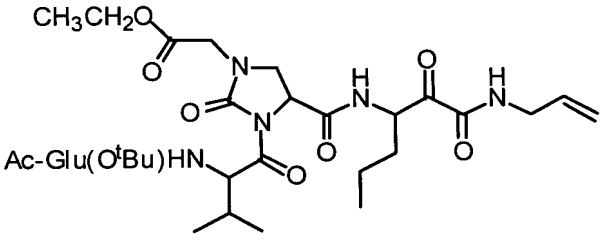

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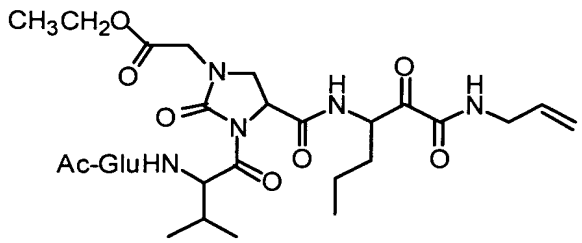

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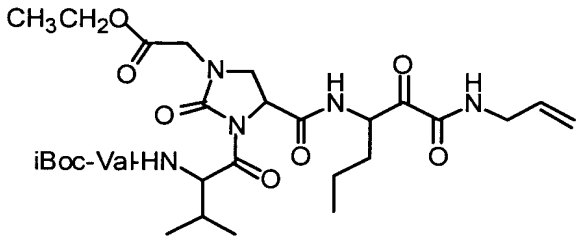

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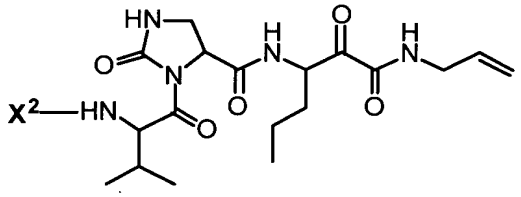
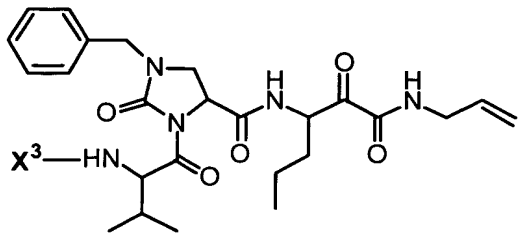
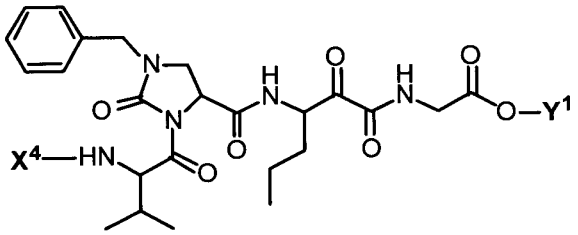


Compound	X^2
9	Boc-Val- (isomer 1)
10	Boc-Val- (isomer 2)
11	Ac-Glu(O^{t}Bu)-Glu(O^{t}Bu)-Val-
12	Ac-Glu-Glu-Val-
13	Boc
14	H

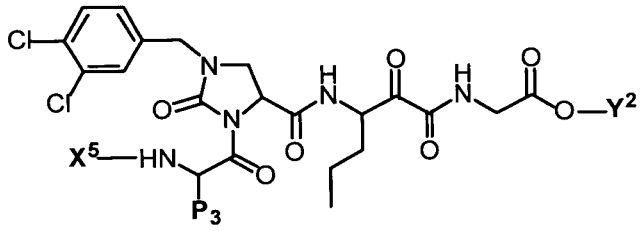


Compound	X^3

15	Boc-Val-
16	Val-
17	Ac-Glu(O^{t}Bu)-Glu(O^{t}Bu)-Val-
18	Ac-Glu-Glu-Val-

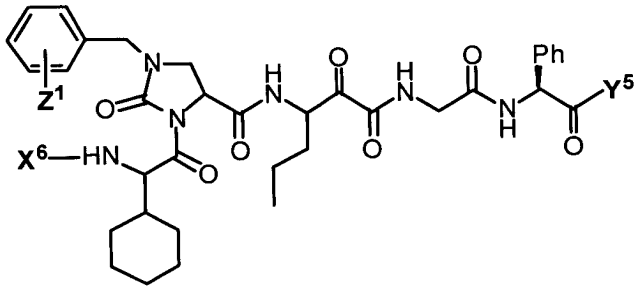


Compound	X^4	Y^1
19	Boc-	allyl
20	H	allyl
21	Boc-Val-	allyl
22	Ac-Glu(O^{t}Bu)-Glu(O^{t}Bu)-Val-	allyl
23	Ac-Glu-Glu-Val-	allyl
24	Boc-Val-	H
25	Ac-Glu(O^{t}Bu)-Glu(O^{t}Bu)-Val-	H

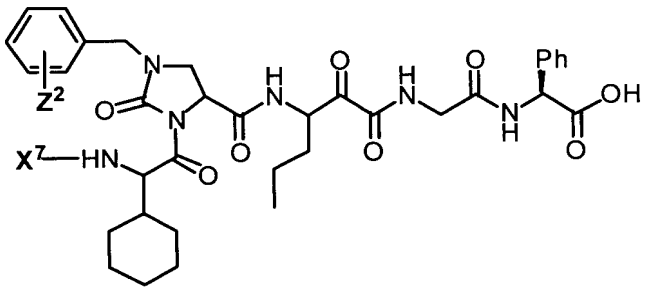


Compound	X^5	Y^2	P_3
26	Boc-Val-	allyl	iPr
27	Ac-Glu(O^{t}Bu)-Glu(O^{t}Bu)-Val-	allyl	iPr
28	Ac-Glu-Glu-Val-	allyl	iPr
29	Boc-	benzyl	Chx

5



Compound	X^6	Z^1	Y^5
30	Boc-	3,4-dichloro	$-NH_2$
31	Boc-	4-Bromo	-OBn
32	Boc-	3-Bromo	-OBn
33	Boc-	4-Chloro	-OBn
34	Boc-	3-Chloro	-OBn
35	iBoc-	3,4-dichloro	$-NH_2$
36	iBoc-	4-Bromo	-OBn
37	iBoc-	3-Bromo	-OBn
38	iBoc-	4-Chloro	-OBn
39	iBoc-	3-Chloro	-OBn
40	Boc-	4-Bromo	-OH
41	Boc-	3-Bromo	-OH
42	Boc-	4-Chloro	-OH
43	Boc-	3-Chloro	-OH
44	iBoc-	4-Bromo	-OH
45	iBoc-	3-Bromo	-OH
46	iBoc-	4-Chloro	-OH
47	iBoc-	3-Chloro	-OH



Compound	X^7	Z^2
48	iBoc-	H
49	Ac-Val-	H
50	iBoc-	3,4-dimethyl
51	Ac-Val-	3,4-dimethyl
52	iBoc-	3-methyl
53	Ac-Val-	3-methyl
54	Ac-Val-	4-methyl
55	Ac-Val-	3-methoxy
56	Ac-Val-	4-methoxy
57	Ac-Val-	4-^{t}-butyl

44. A pharmaceutical composition for treating disorders associated with the HCV protease, said composition comprising therapeutically effective amount of one or more compounds in claim 43 and a pharmaceutically acceptable carrier.

45. The pharmaceutical composition of claim 44, additionally containing an antiviral agent.

46. The pharmaceutical composition of claim 44 or claim 45, still additionally containing an interferon.

47. The pharmaceutical composition of claim 46, wherein said antiviral agent is ribavirin and said interferon is α-interferon.